Artificial Ion Channels

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Highly Selective Artificial Cholesteryl Crown Ether K^+-Channels

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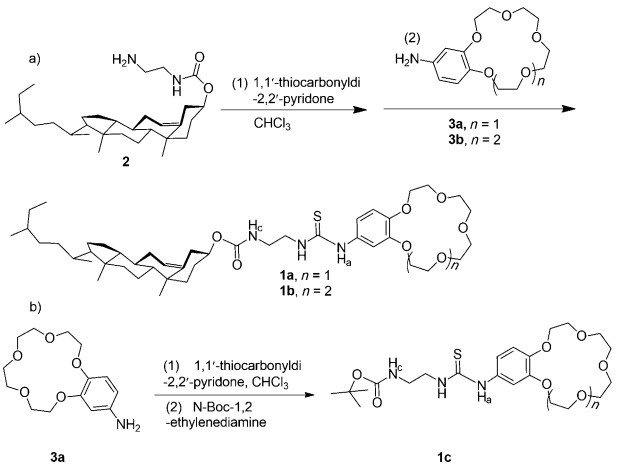
Abstract: *The bacterial KcsA channel conducts K^+ cations at high rates while excluding Na^+ cations. Herein, we report an artificial ion-channel formed by H-bonded stacks of crown-ethers, where K^+ cation conduction is highly preferred to Na^+ cations. The macrocycles aligned along the central pore surround the K^+ cations in a similar manner to the water around the hydrated cation, compensating for the energetic cost of their dehydration. In contrast, the Na^+ cation does not fit the macrocyclic binding sites, so its dehydration is not completely compensated. The present highly K^+-selective macrocyclic channel may be regarded as a biomimetic of the KcsA channel.*

The exchange of ions across the lipid bilayer membrane is a prerequisite for many physiological processes.[1,2] Natural ion channels play significant roles in supporting the metabolism of living cells, and their dysfunction can lead to a number of diseases, even death.[3] Among ion channels, the KcsA K^+ channel is highly selective for K^+ cations. It has a hydrophobic conical pore and the selectivity filter in the middle, affording closely spaced carbonyl sites for the selective coordination of the dehydrated K^+ cations.[4]

Biomimetic approaches have been used to develop artificial supramolecular channels with the hope to reach the high selectivity of the KcsA channel.[5–7] Barrel-stave systems,[8] G-quadruplex,[9] lariat crown ethers,[10] hydraphiles[11] or peptide-appended crownethers[12,13] have been intensively used to construct ion-channels for selective ionic translocation. We are interested in the possibility to self-organize heteroditopic ureido crown ethers through H-bonding for suitable membrane ion channel transport functions.[14] This approach has been extended to light-responsive channels, and the structure–activity relationships have been determined.[15] We know from our previous studies, that lipophilic ureido crown ethers disrupt the bilayer membrane at low concentration, showing rare single channel openings. At higher concentration, a rich array of interconverting channel conductance states are observed for K^+ cations. The channels arise from H-bonded stacks of crown ethers where transport of cations would occur by the macrocycles around a central large pore.[14b] Within this context we presumed that the entropic cost of cation binding/transport must be far larger than the case where these macrocyclic receptors present a restricted conformational entropy in the bilayer. Their self-assembly can influence their dynamic distribution and the stability of the channels within the bilayer membrane. Within this context, steroids are important cyclic compounds,[16] intensively used in the construction and stabilization of many ion channel superstructures.[16–18] Based on these observations, we designed and prepared in this study, a series of cholesteryl-thioureido-ethylamide crown ethers that self-assemble into robust ion-channels and show a remarkably high selectivity for the K^+ against Na^+ cations, close to that of natural channels. The thioureido-ethylamide linker connecting crown ether and cholesterol moieties form H-bonded arrays of channel-type stacks of crown ethers disposed in very close proximity pointing towards the center of the channel and expected to serve as ion selectivity filters.[19] Cholesterol moieties aiming to stabilize the channels, act as anchoring arms inducing low diffusivity, clustering, and higher preorganization of the macrocycles in lipid bilayers.[20]

The synthesis of key compounds **1a–c** is presented in Scheme 1. 3β-Cholest-5-en-3-yl-*N*-(2-*a*minoethyl) carbamate



Scheme 1. Synthesis of a) cholesteryl thioureidoethylamide-15-crown-5-ether **1a**, and cholesteryl thioureidoethylamide-18-crown-6-ether **1b** and b) of the reference *tert*-butylthioureidoethylamide-15-crown-5 ether, **1c**.

2 was prepared according to the literature[21] and then converted to 3β-cholest-5-en-3-yl-*N*-(2-isothiocyanatoethyl)-carbamate,[22] which was reacted in situ with the corresponding 4-amino-benzo-crown-ethers **3a**/**3b**, to provide cholesteryl-thioureido-ethylamide crown ethers **1a** and **1b**. The macrocyclic heads are benzo-15-crown-5 in **1a** and benzo-18-

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